SHORT COMMUNICATION

Myocardial electrical instability after abrupt withdrawal of long-term administration of propranolol to guinea pigs

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Summary

1. Abrupt termination of chronic propranolol therapy has been suggested to cause a ‘rebound’ phenomenon. To investigate this possibility guinea pigs were given propranolol orally for 21 days.

2. At various times over a 10 day period after the last dose hearts were removed and subjected to aerobic perfusion, ischaemia and reperfusion. Rhythm disturbances were measured and compared with corresponding values in control hearts from the control untreated animals.

3. Three to 6 days after termination of drug administration a pronounced increase in myocardial electrical instability was observed. During pre-ischaemic aerobic perfusion the incidence of arrhythmias was increased and during reperfusion the incidence of ventricular fibrillation rose dramatically.

Key words: arrhythmia quantification, chronic β-adrenoreceptor blockade, heart, propranolol-withdrawal syndrome.

Introduction

Several clinical case reports have suggested that abrupt discontinuance of propranolol after prolonged therapy may result in myocardial infarction (Slome, 1973), exacerbation of angina (Alderman, Coltart, Wettach & Harrison, 1974) and development of malignant ventricular arrhythmias (Olsen, Miller, Amsterdam, Wood, Brocchini & Mason, 1975). However, although the existence of the propranolol-withdrawal syndrome is generally accepted a number of negative reports exist (Patano & Lee, 1976; Myers & Horwitz, 1978; Shiroff, Mathis, Zelis, Schneck, Babb, Leaman & Hayes, 1978). Some explanation for this conflict may reside with the complexities associated with the use of patient or in vivo studies. In these studies any number of factors, ranging from patient case history to endogenous sympathetic drive, may influence the incidence and/or timing of this transient phenomenon. To avoid these problems, we investigated the effect of propranolol withdrawal on the incidence of rhythm disturbances in perfused hearts isolated from guinea pigs that had been taken off long-term propranolol treatment.

Methods

Animals

Male guinea pigs (350–500 g) of the Duncan–Hartley strain were used. DL-Propranolol (ICI Ltd) was given orally. The β-adrenoreceptor-blocking drug was added to the diet so that, on average, guinea pigs consuming 63 g of laboratory chow/day received 4 mg of propranolol/kg body weight. Propranolol was given for a period of 21 days and animals were killed at 0, 1, 2, 3, 4, 6 and 10 days after withdrawal of propranolol. The effect of propranolol withdrawal on myocardial electrical stability was determined in perfused hearts isolated from these animals.

Perfusions

Aerobic retrograde perfusion was conducted at a perfusion pressure of 44 mmHg and a temperature of 37°C. Coronary flow rates were 6–9 ml
min$^{-1}$ g$^{-1}$ wet weight. During ischaemia (when coronary fluid was infused at a constant rate of 0.9 ml/min) coronary flow rates were reduced to 0.5–0.7 ml min$^{-1}$ g$^{-1}$ dry weight.

**Perfusion medium**

This was a modified Krebs–Henseleit bicarbonate buffer of the following composition (mmol/l): sodium chloride, 119; sodium bicarbonate 25; potassium chloride 2.4; potassium dihydrogen phosphate 0.6; magnesium sulphate 1.2 and calcium chloride 2.5. When gassed with $O_2 + CO_2$ (95:5, v/v) the pH of this buffer was 7.4 at 37°C. Before use, all perfusion fluids were passed through a cellulose acetate filter of pore size 5.0 µm.

**Perfusion time sequence**

To minimize differences among hearts in terms of reserves of endogenous substrates and to allow time for washout of unbound propranolol, all hearts were perfused initially for 30 min with bicarbonate buffer in the absence of substrate. During this time preparation stability was assessed. If heart rates were constant (215 ± 2.6 beats/min) and sinus rhythm was regular, with no or only minimal incidence of ectopic activity (rhythm disturbance unit < 6.0), hearts were perfused for a further 30 min with medium containing sodium pyruvate (10 mmol/l); a substrate which has been shown previously (Dennis, Hearse & Coltart, 1979) to be associated with a high incidence of reperfusion rhythm disturbances. To precipitate reflow arrhythmias this latter period of perfusion, in the presence of pyruvate, was subdivided into 10 min of aerobic perfusion followed by 10 min of ischaemia and then 10 min of reperfusion.

**Rhythm analysis**

Quantitative assessment of the incidence of spontaneous ventricular-rhythm disturbances during aerobic perfusion, ischaemia and reperfusion was carried out by using a computer-aided arrhythmia analysis system that has been developed in this laboratory. This system, which has been described previously (Dennis, Stoate & Waldron, 1979), assesses the severity of rhythm disturbances through statistical determinations of standard deviations of beat intervals. To minimize standard deviations arising from changes in heart rate 1 min sets of results were grouped and then subjected to one-tailed analysis of variance. Residual standard deviation (derived from the difference between total variation and between set variation) was then expressed as a percentage of the group mean. This expression was utilized as the rhythm disturbance unit.

**Results**

The results of the analysis of rhythm in hearts removed from animals at various times throughout a 10 day period after abrupt withdrawal of propranolol are shown in Fig. 1. Different temporal changes in the ability of these hearts to maintain normal sinus rhythm were seen under each perfusion condition.

**Aerobic perfusion**

During the period of adequate perfusion, before the ischaemic period, the frequency of

![Fig. 1. Withdrawal of long-term propranolol: effect on incidence of rhythm disturbances in isolated perfused guinea-pig hearts. The results shown are the quantitative assessments of rhythm disorders during (a) aerobic perfusion, (b) ischaemia and (c) reperfusion of hearts removed from animals that either had not been given propranolol (controls) or had been taken off β-adrenoreceptor blockade for the indicated periods of time. Rhythm unit values, representing frequency and severity of aberrant contractions, are the means ± SEM from 12 control heart perfusions and five hearts for each experimental group. Incidence of ventricular fibrillation is not included in the rhythm unit results: this is represented by the cross-hatched histogram. Statistical significance (non-paired Student's t-test): *$P < 0.05$; **$P < 0.02$; ***$P < 0.005$.](image-url)
premature ventricular and ectopic beats was increased above control values at 3–6 days after the withdrawal of propranolol.

Ischaemia

In contrast, during ischaemia the incidence of rhythm disturbance was increased relative to control values in hearts removed from animals still receiving propranolol. However, after cessation of drug administration the frequency of ectopic and premature beats returned to control values and in addition there was a dramatic increase in the occurrence of ventricular fibrillation. As in the case of the rhythm disturbances seen during pre-ischaemic aerobic perfusion, incidence of fibrillation upon postischaemic reflow was at a maximum 3–6 days after withdrawal of propranolol.

Reperfusion

During reperfusion, the incidence of ectopic and premature beats was high in hearts from control animals and these rhythm disturbances were significantly reduced in hearts taken from animals on propranolol. However, after cessation of drug administration the frequency of ectopic and premature beats returned to control values and in addition there was a dramatic increase in the occurrence of ventricular fibrillation. As in the case of the rhythm disturbances seen during pre-ischaemic aerobic perfusion, incidence of fibrillation upon postischaemic reflow was at a maximum 3–6 days after withdrawal of propranolol.

Discussion

These results indicate that pretreatment with propranolol protected against arrhythmias during the reperfusion period for up to 24 h after dosing. However, abrupt propranolol withdrawal caused a paradoxical increase in myocardial electrical instability. At 3–6 days after the end of drug administration the extent of rhythm disturbances during aerobic perfusion and, more important, incidence of fibrillation during reperfusion were much greater than would be expected in control hearts removed from animals which had not been subject to β-adrenoreceptor blockade.

The suggestion that abrupt discontinuation of propranolol causes a rebound effect in guinea-pig hearts is consistent with the reports of an investigation of propranolol effects on rat hearts in vitro (Glaubiger & Lefkowitz, 1977). In these studies it was demonstrated that giving a β-adrenoreceptor antagonist increases the number of β-adrenoreceptors. Increased sensitivity of cardiac tissue to catecholamines, which has also been clinically observed (Nattel, Rangno & Van Loon, 1978), could provide a potential explanation for the increased incidence of rhythm disturbances. Such a mechanism would involve enhanced production of cyclic AMP, a possible determinant of cardiac vulnerability to ventricular fibrillation (Opie, Nathan & Lubbe, 1979) in response to increased β-adrenoreceptor stimulation from released endogenous catecholamines. Such a drug-induced physiological rebound would also increase myocardial oxygen consumption and, through a worsening of the coronary oxygen supply and demand equation, aggravate ischaemic events.

In conclusion, the existence in the guinea pig of a propranolol ‘rebound’ has been established and a mechanism proposed. Cautiously extrapolating from the guinea-pig heart to the clinical situation it is conceivable that, after abrupt withdrawal of propranolol, transient but serious aggravation of reperfusion arrhythmias (which in man may result from release of coronary artery spasm or platelet disaggregation) may explain in part the increased incidence of sudden death (Olsen et al., 1975) after abrupt propranolol withdrawal.

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References


